Pharmacogenomics: A New Age for Drug Therapy or Unrealistic Hype?

Kenneth Thummel, PhD

Department of Pharmaceutics

University of Washington

Pharmacogenomics

Hereditary Basis
for Interindividual Differences
in Drug Response

Pharmacogenetics with 2 SNPs

PHARMACOGENETICS
PHARMACOGENOMICS

Urs Meyer, 2001

Efficacy of Drug Therapy

It is unusual for a drug to work optimally in every subject; 20-75% of subjects in 14 major clinical trials appeared to derive no clinical benefit from treatment.

Individualized Therapy

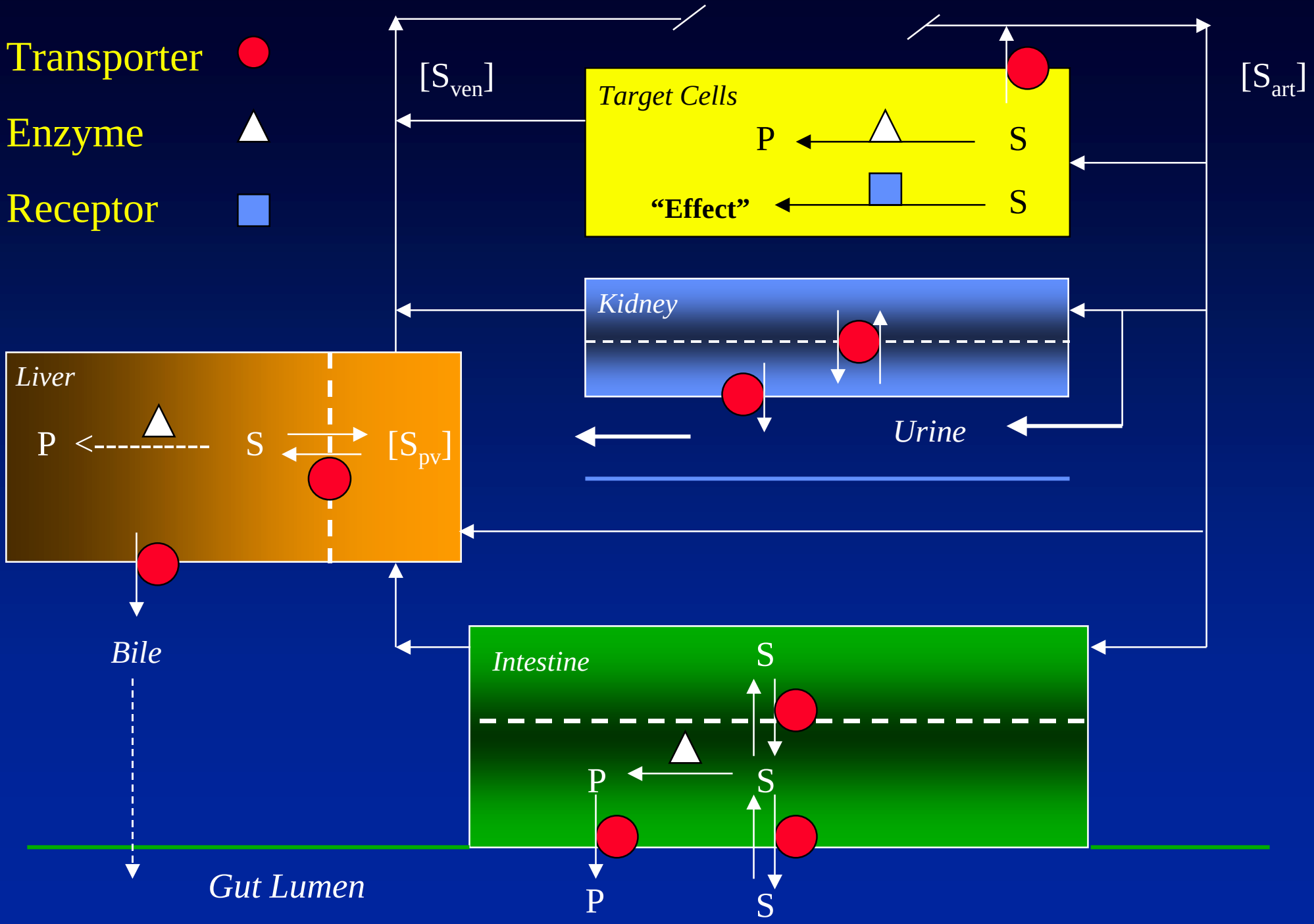
Evans et al, SJCRH, 2000

Polygenic Nature of Drug Effects

- Disease Pathogenesis Genes
- Host Susceptability Genes

- Drug Metabolism
- Drug Transport

- Drug Receptor
- Drug Target


Transporter
Enzyme
Receptor
[S ven]
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Target Cells
P
S
"Effect"
S
Kidney
Urine
Liver
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Bile
Intestine
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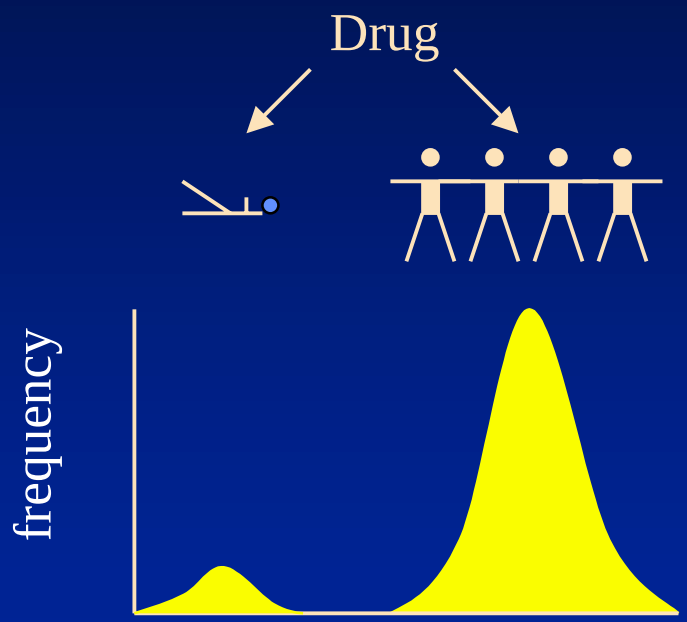
P
S
Gut Lumen

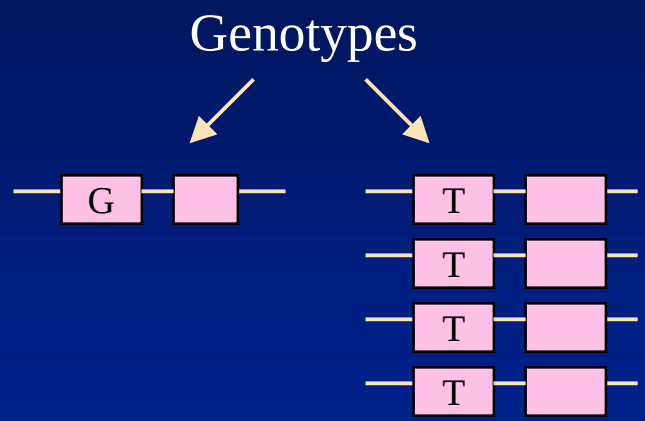
Pharmacogenomic Discovery

Pre-Genomics



Identify Genotype(s)

Post-Genomics

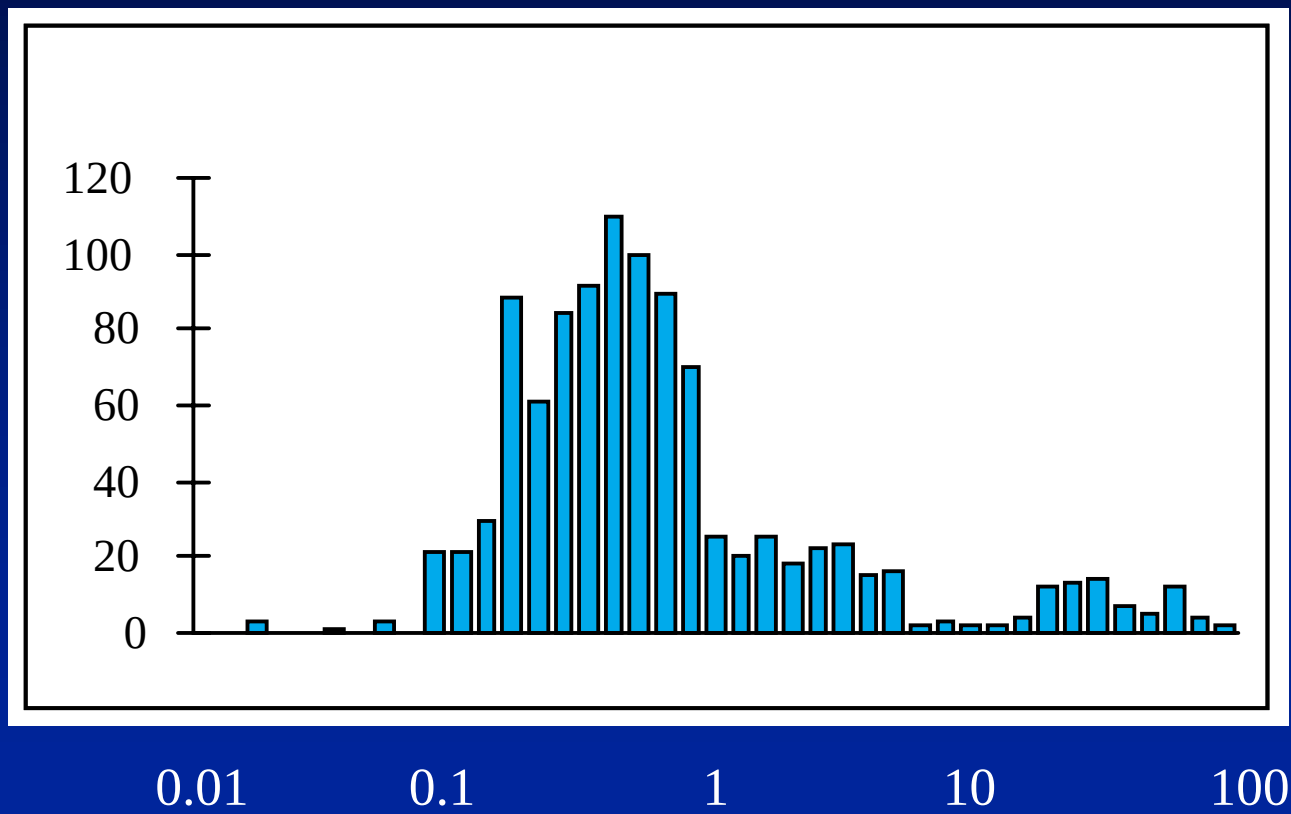


Identify Phenotypes

Adapted from W. Evans, St. Jude

CYP2D6 Polymorphic Metabolism

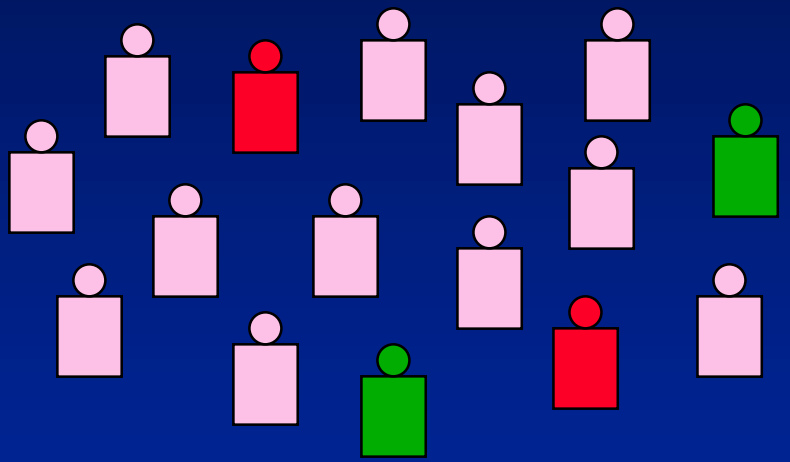
debrisoquine → 4-hydroxy debrisoquine

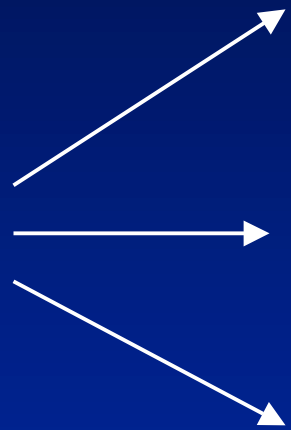


(adapted from Dahl et al., Pharmacogenetics 3:61, 1993)

Empirical Strategy for Drug Therapy

Treat all Patients with the same Diagnosis
with the Same Medication
and Same Starting Dose





Responders

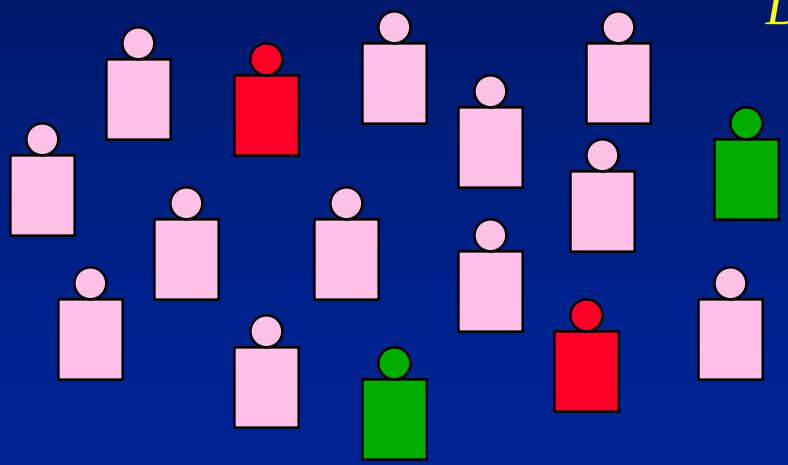
Nonresponders

Toxicity (ADR)

Adverse Drug Reactions(ADRs) are the fourth leading cause of hospitalization and fifth leading cause of mortality in the USA.

Adapted from W. Evans, St. Jude

Promise of Pharmacogenomics: Genetic Stratification



Drug Selection

#1

Remove patients unlikely to respond and those at risk for ADR.

#2

Treat those most likely to respond and least likely to exhibit ADR.

Dose Adjustment

#3

Tailor initial dose to genotype and predicted phenotype.

Adapted from W. Evans, St. Jude

Application of Pharmacogenomics: Factors to Consider

- » Ease of identifying responders (efficacy or toxicity)
- Therapeutic range (minimum toxic/minimum effective)
- Therapeutic alternatives (within class or alternate class)
- Genetic penetrance (prediction of phenotype)
- Specificity of the test (should be very high)
- Clinical alternatives (therapeutic monitoring)
- Cost-benefit of the test (clinical practice)
- E˚ LSI considerations (privacy, discrimination)

Application of Pharmacogenomics: Factors to Consider

- Ease of identifying responders
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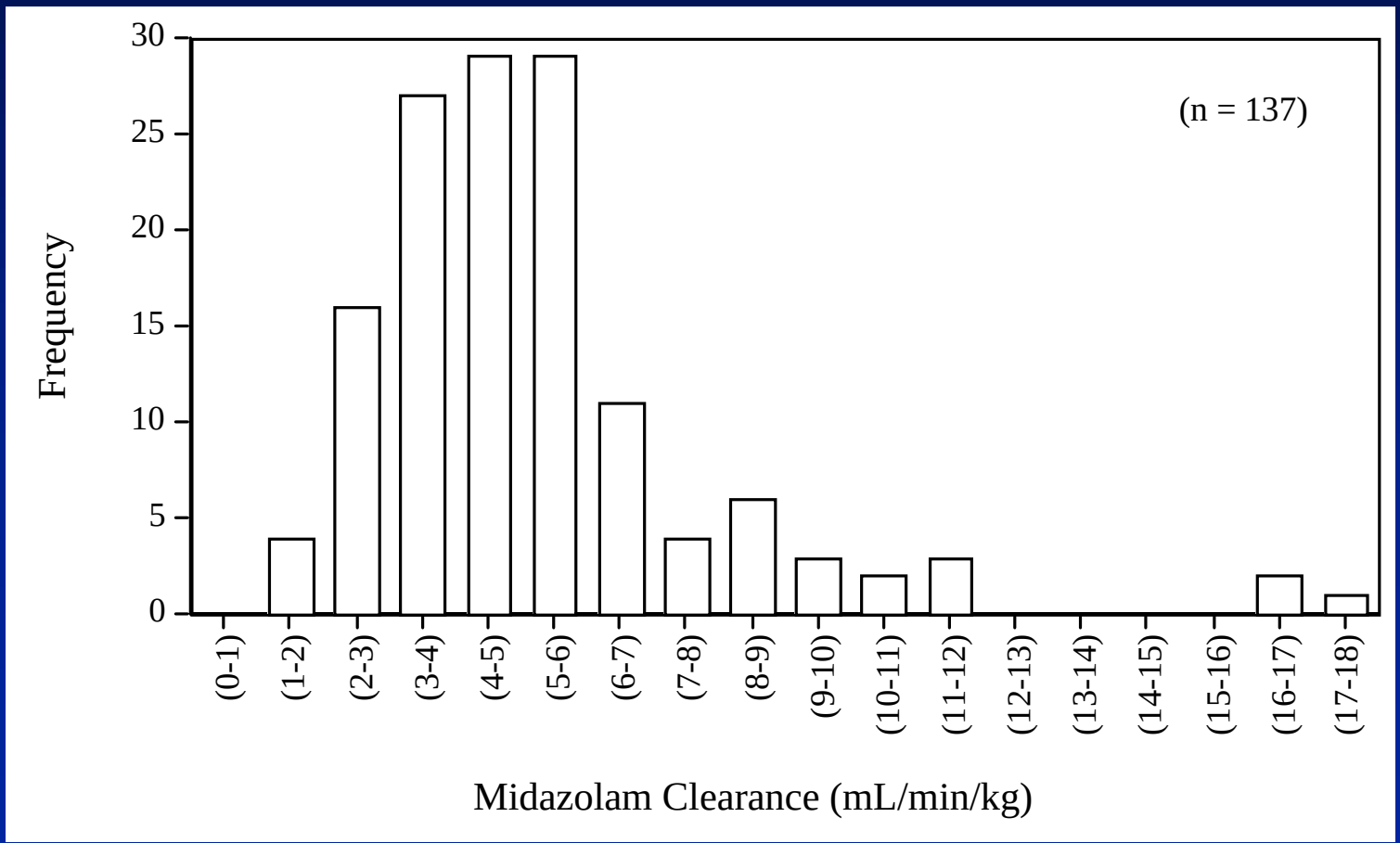
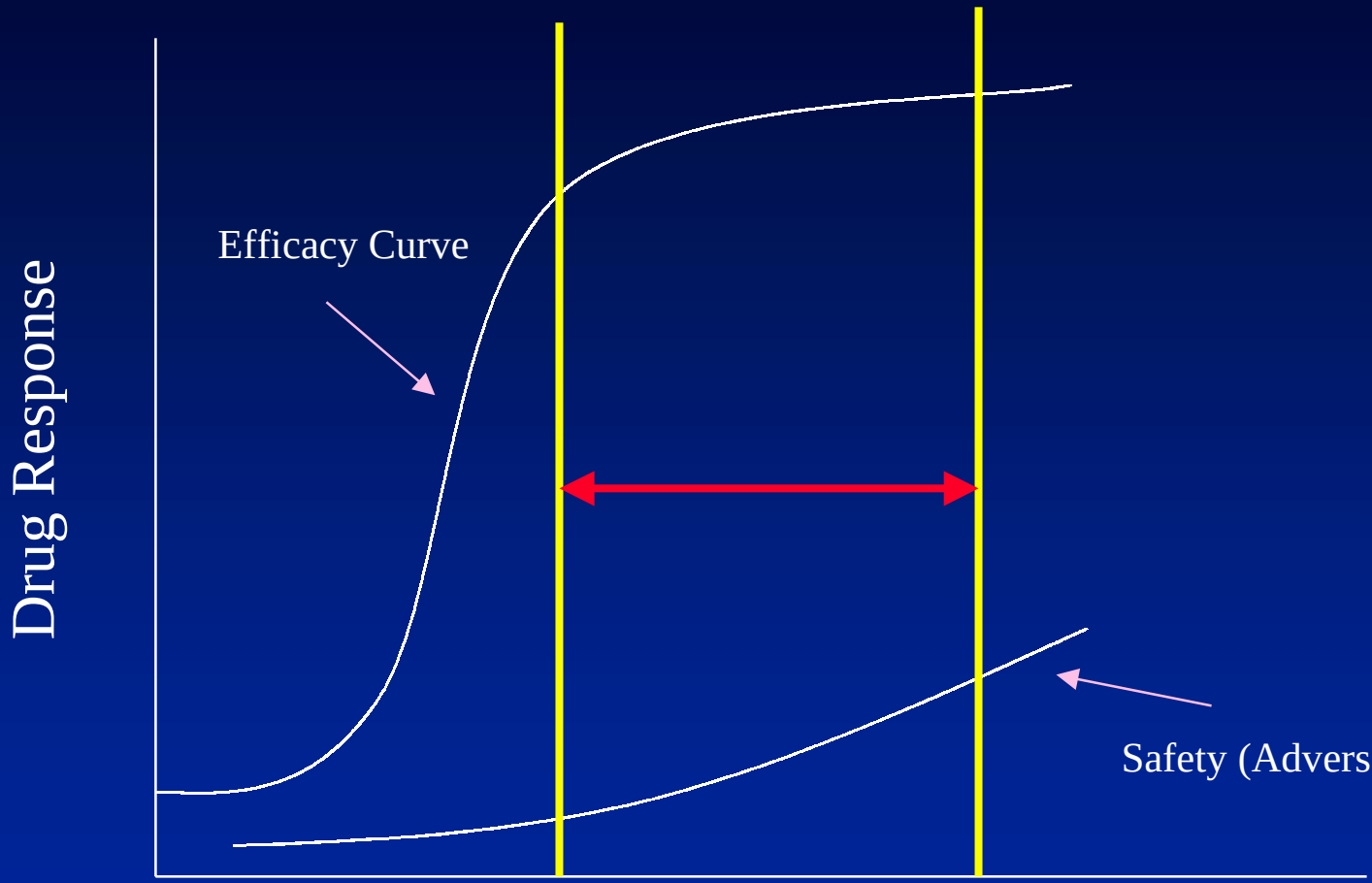
Inter-Individual Variability in Drug Exposure

Midazolam $\xrightarrow{\text{CYP3A4/5}}$ 1’-OH, 4-OH Midazolam

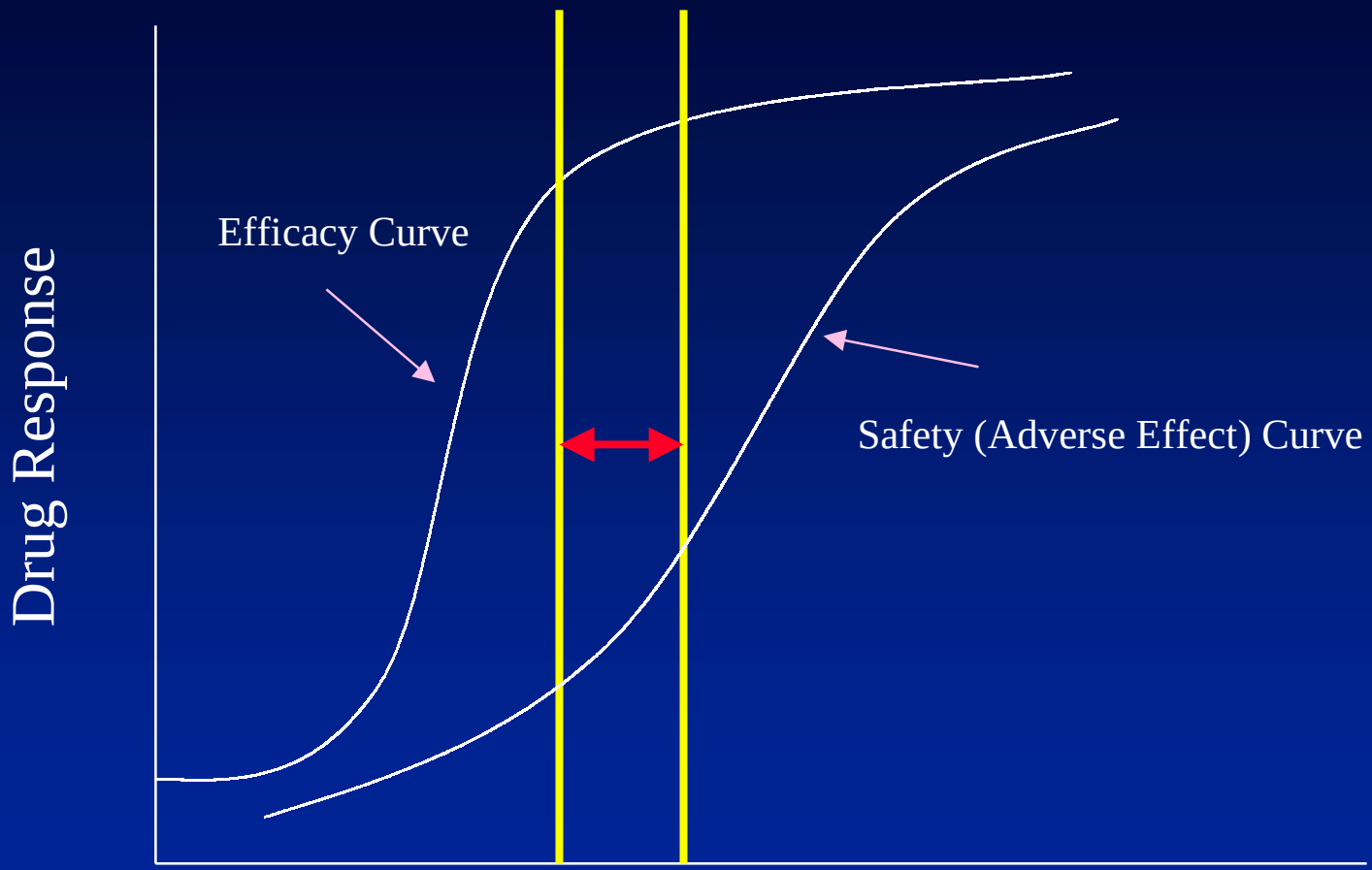


Wide Therapeutic Range



Adapted from S-M. Huang/FDA

Narrow Therapeutic Range



Adapted from S-M. Huang/FDA

One can anticipate that the most cost-effective application for pharmacogentic testing will be for narrow therapeutic range drugs.

Examples:

- warfarin - CYP2C9 - anticoagulation
- 6-mercaptopurine - TPMT - leukemia
- propafenone - CYP2D6 - arrhythmias
- neuroleptics - CYP2D6 - psychiatric disorders

Thiopurine Methyl Transferase Gene (TPMT)

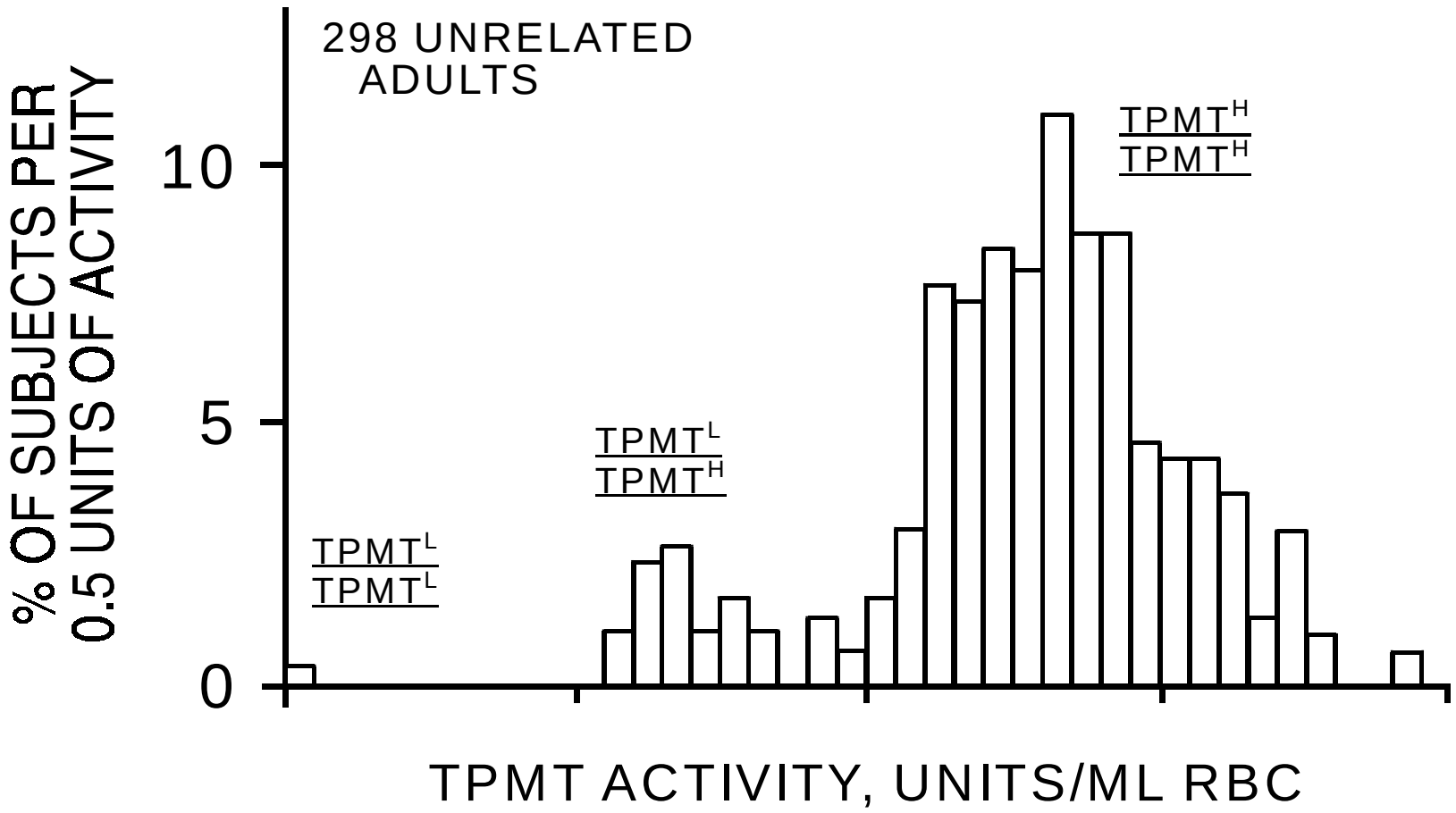
TPMT catalyzes metabolism of thiopurine and thioguanine anti-cancer drugs

- only pathway for elimination in WBCs

- Intermediate Metabolizers: 10%
- Poor Metabolizers: 1/300

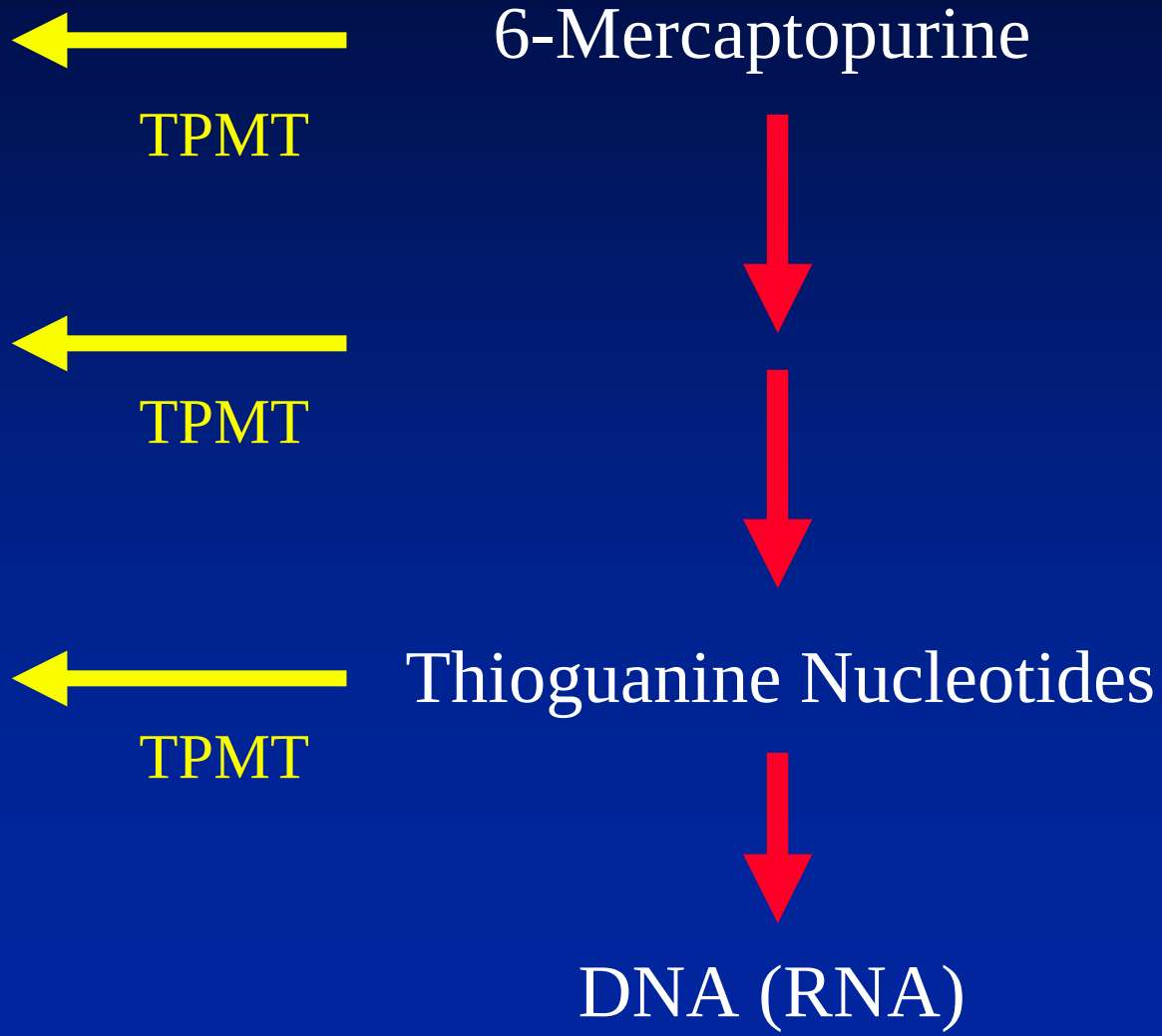
Relling et al., J. Natl. Cancer Inst. 91:2001-08, 1999

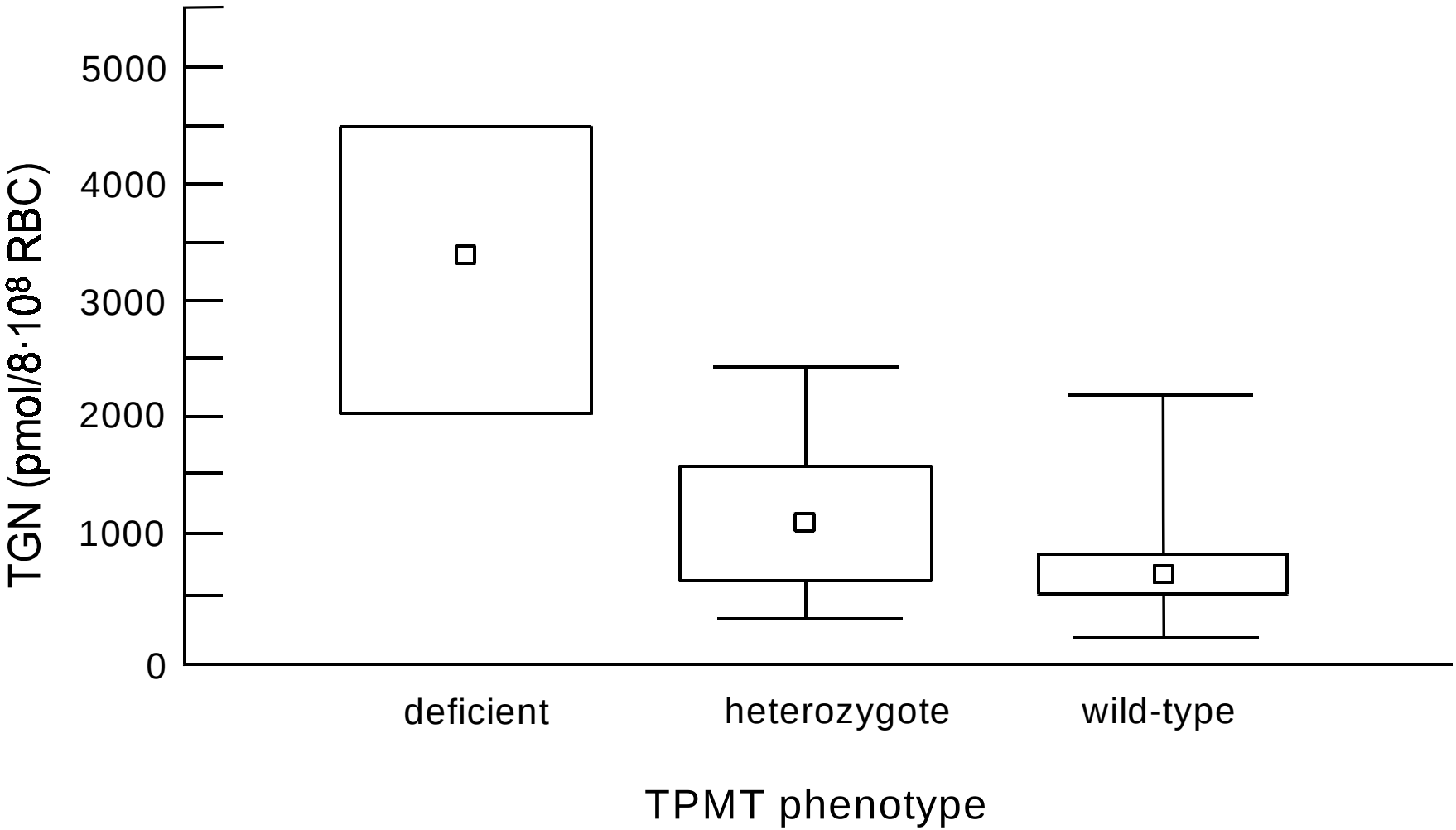
HUMAN RBC TPMT



Weinshilboum and Sladek
Am J Hum Gen 32(5):651-62, 1980

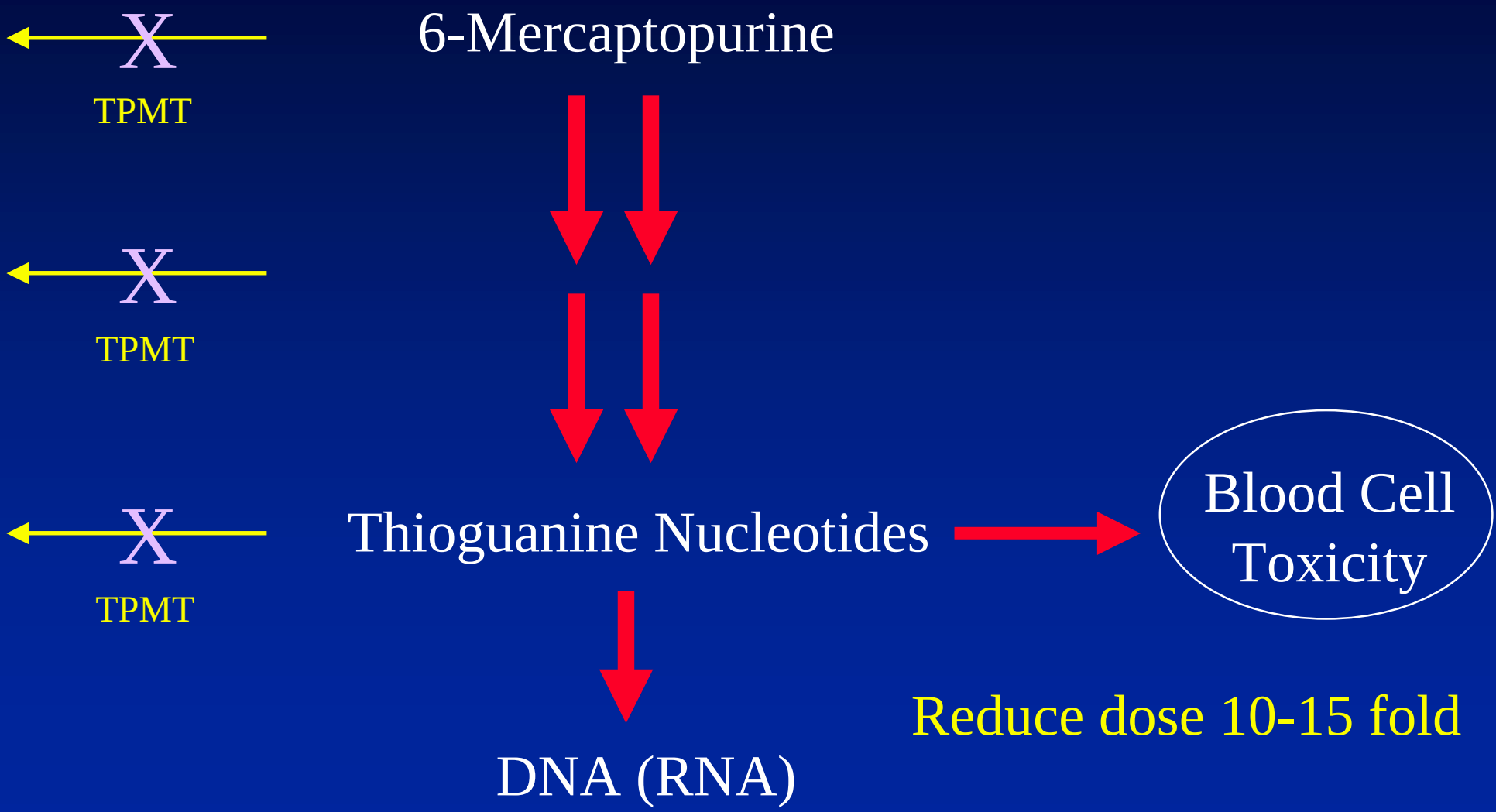
Thiopurine Drugs and Childhood Leukemia



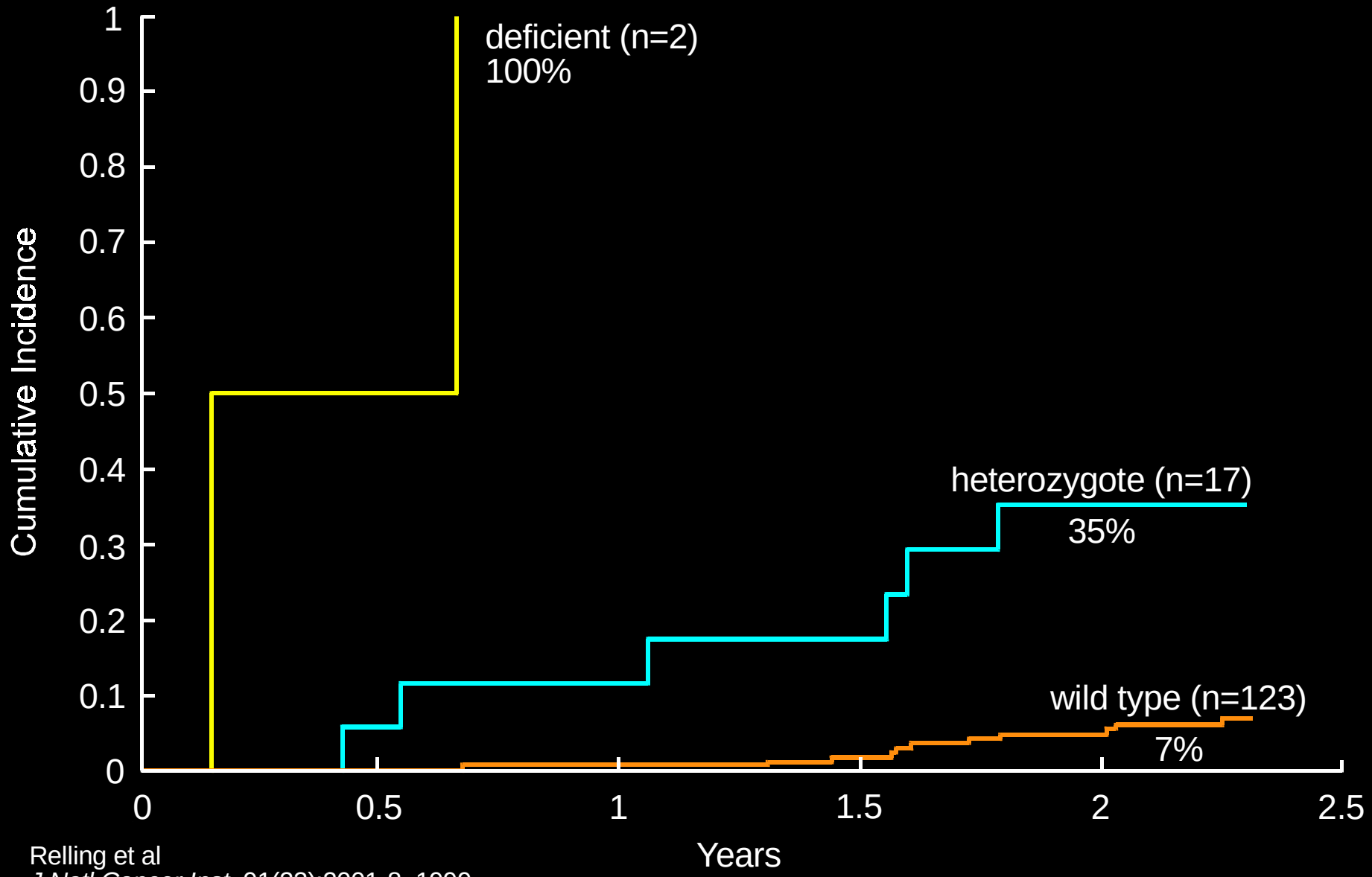


Krynetski and Evans
Pharm Res 16(3):342-9, 1999

TPMT Deficiency and 6-MP Safety/Toxicity



Cumulative Incidence of 6mp Dose Alterations to Prevent Toxicity During Continuation Therapy of Total XII



Relling et al
J Natl Cancer Inst. 91(23):2001-8, 1999

TPMT Deficiency and ALL Treatment

Cost -Benefit

- screen 10 to benefit 1 IM or PM patient
- reduce morbidity and mortality
- on call testing *vs* batch testing

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Asthma: β_2-Adrenergic Receptor SNP

- β_2 receptor mediates bronchodilation in response to agonists
- Mutiple mutations in the β_2 -receptor gene; two loci encode an amino acid change;

Gly(16)Arg and *Gln(27)Glu*

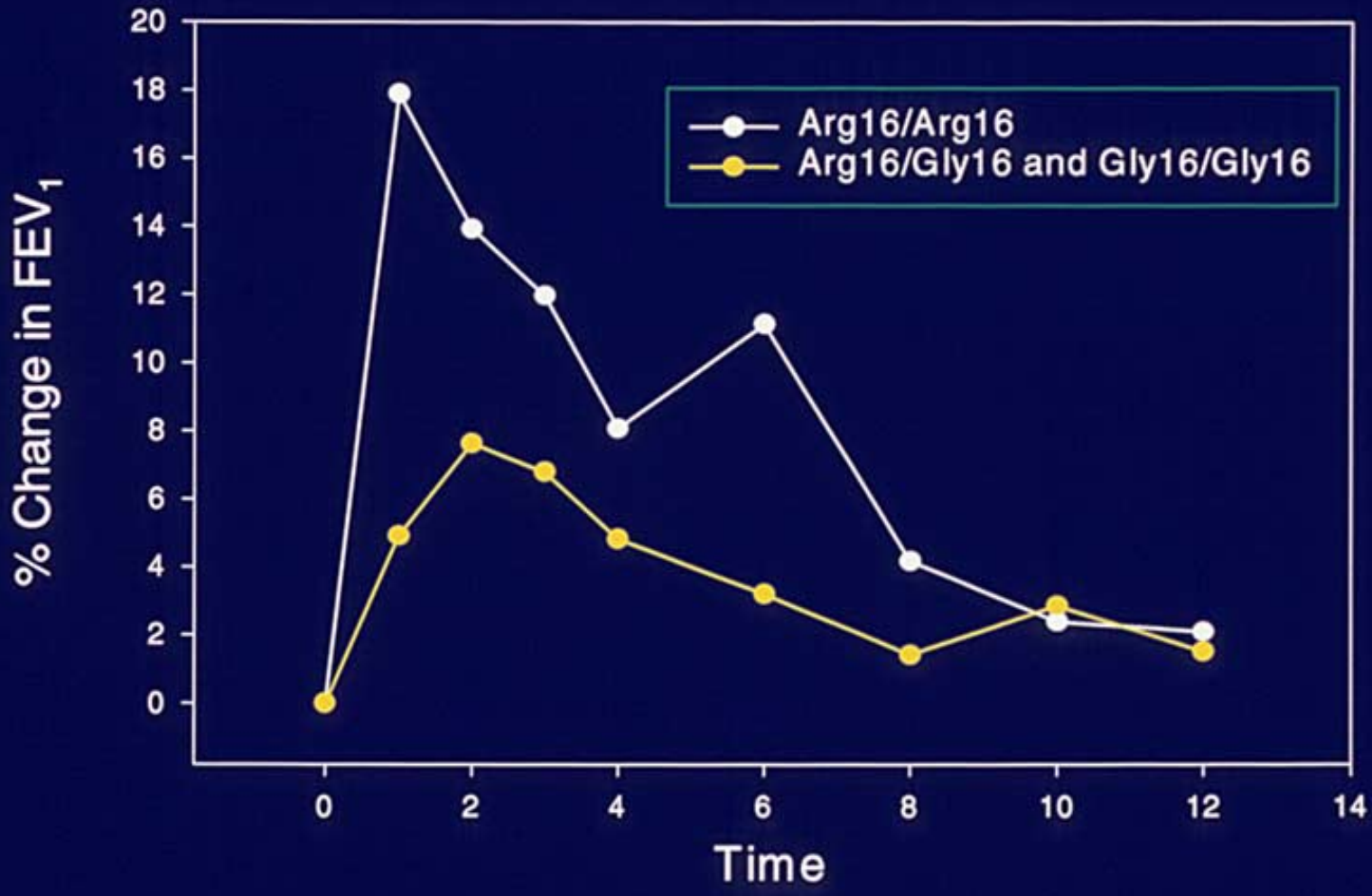
Arg-16/Arg-16: 15% of population

Arg-16/Gly-16: 38% of population

Gly-16/Gly-16: 45% of population

FEV1 response to albuterol by β_2AR genotype

Lima, et al. Clin Pharmacol Ther 1999;65:519



One can identify patients who might derive the greatest benefit from inhaled or oral β-agonists, but will it be cost effective?

- Alternative treatment options
- Emperical dosing and monitoring efficacy

Other Examples:

- Angiotensin converting enzyme - ACE inhibitors (enalapril)
- α-adducin protein - thiazide diuretics (chlorothiazide)
- APOE - cholinesterase inhibitor (tacrine)
- ALOX5 - leukotriene synthesis inhibitors (zileuton)
- BRCA1/2 - estrogen receptor inhibitors (tamoxifen)

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SNPs and Pharmacodynamic Effect

- Inter-individual differences in drug response can often be attributed to differences in circulating blood concentration (C_{ss})
- C_{ss} is inversely related to drug clearance
- Oral drug clearance can vary considerably

Pathways of Drug Elimination

Excretion

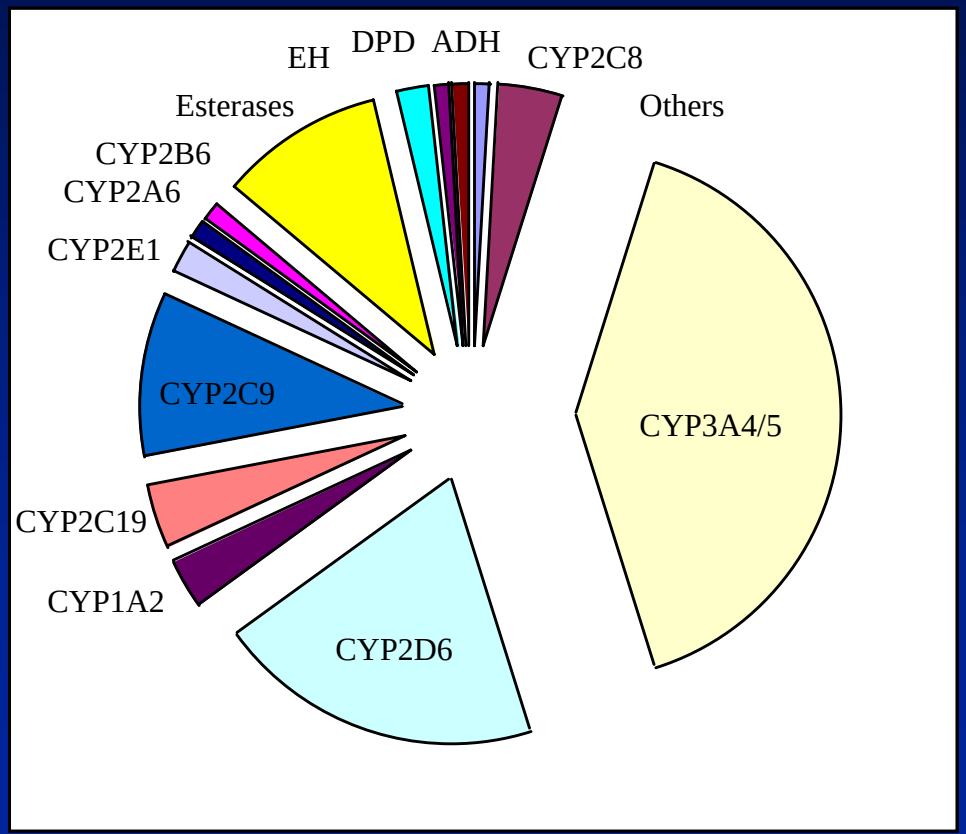
- urinary efflux
- biliary efflux
- intestinal efflux

Biotransformation

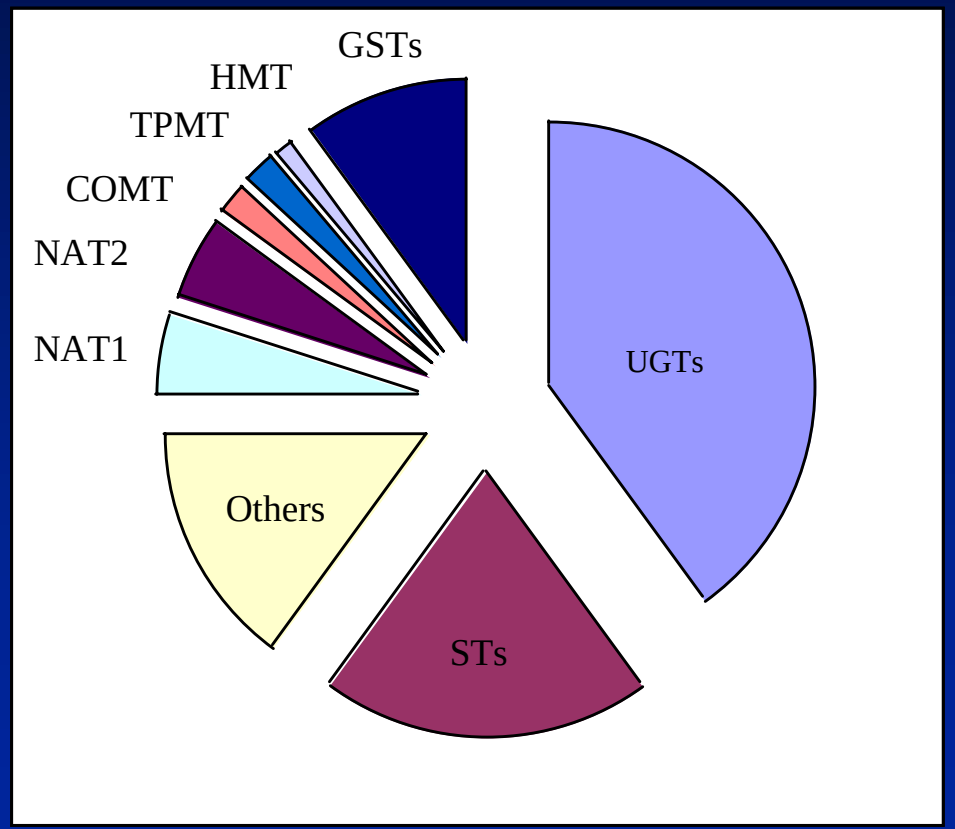
- tissue enzymes
- bacterial flora enzymes

Enzyme Contributions to Drug Metabolism

PHASE I

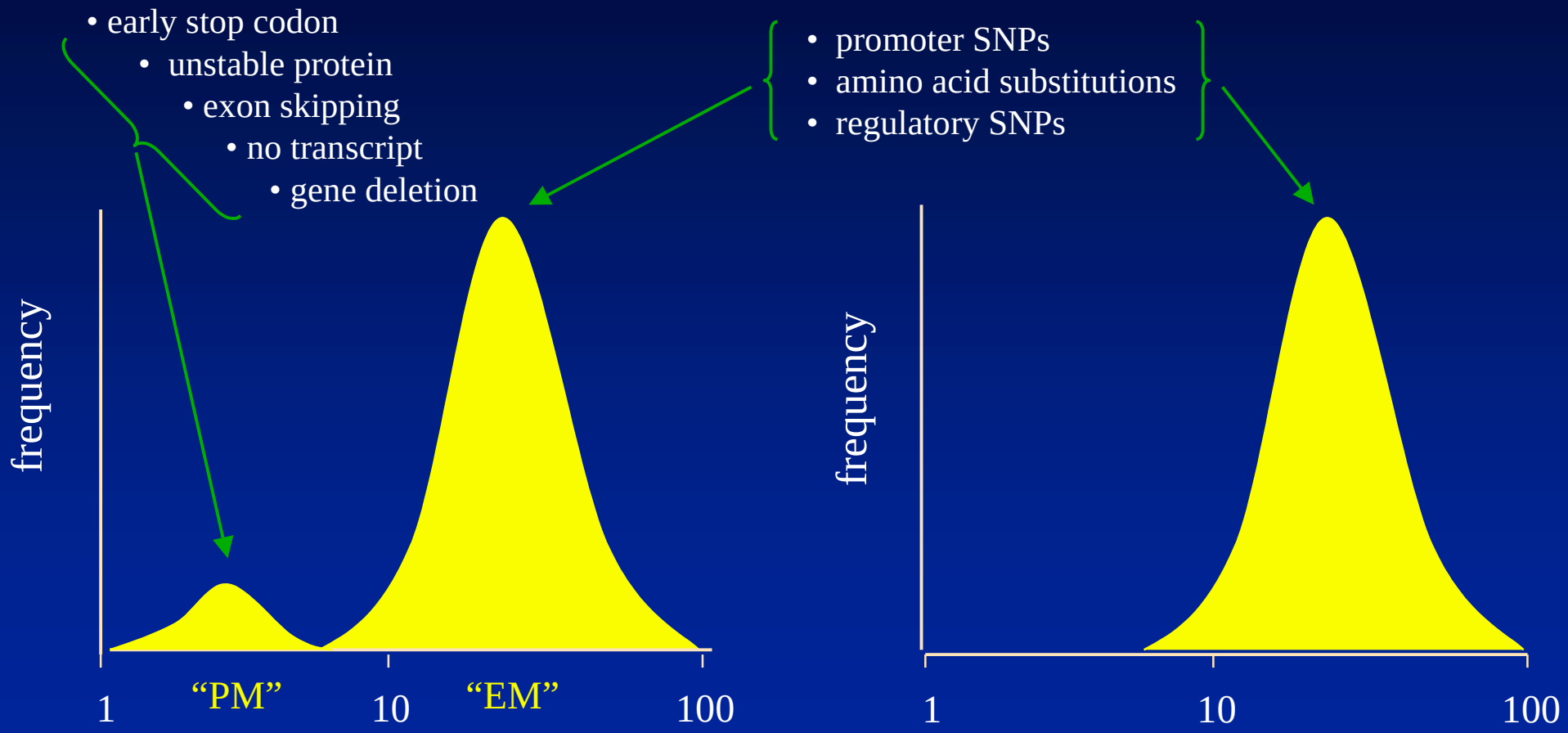


PHASE II



Adapted from W. Evans, St. Jude

Character of Population Phenotype - Genotype



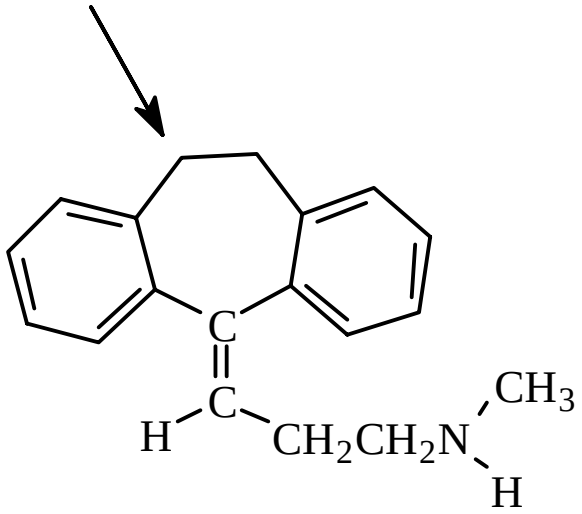
Adapted from W. Evans, St. Jude

Important P450 Genotypes: Drug Disposition

	# allelic variants	homozygous PM
CYP2C9	7 (Cys_{144}, Leu_{359})	~ 0.3-1%
CYP2C19	5 (m1 - m5)	3-5% (C), 20% (A)
CYP2D6	22 (5 common)	5-10% (C), 1% (A)
CYP3A5	2 (splicing variants)	72% (C), 42% (A)

For more information, see: *http://www.imm.ki.se/CYPalleles*

CYP2D6 Polymorphism: Nortriptyline Kinetics



CYP2D6 → E-10-hydroxy nortriptyline

(bold: dominant, CYP2D6-mediated metabolite in urin

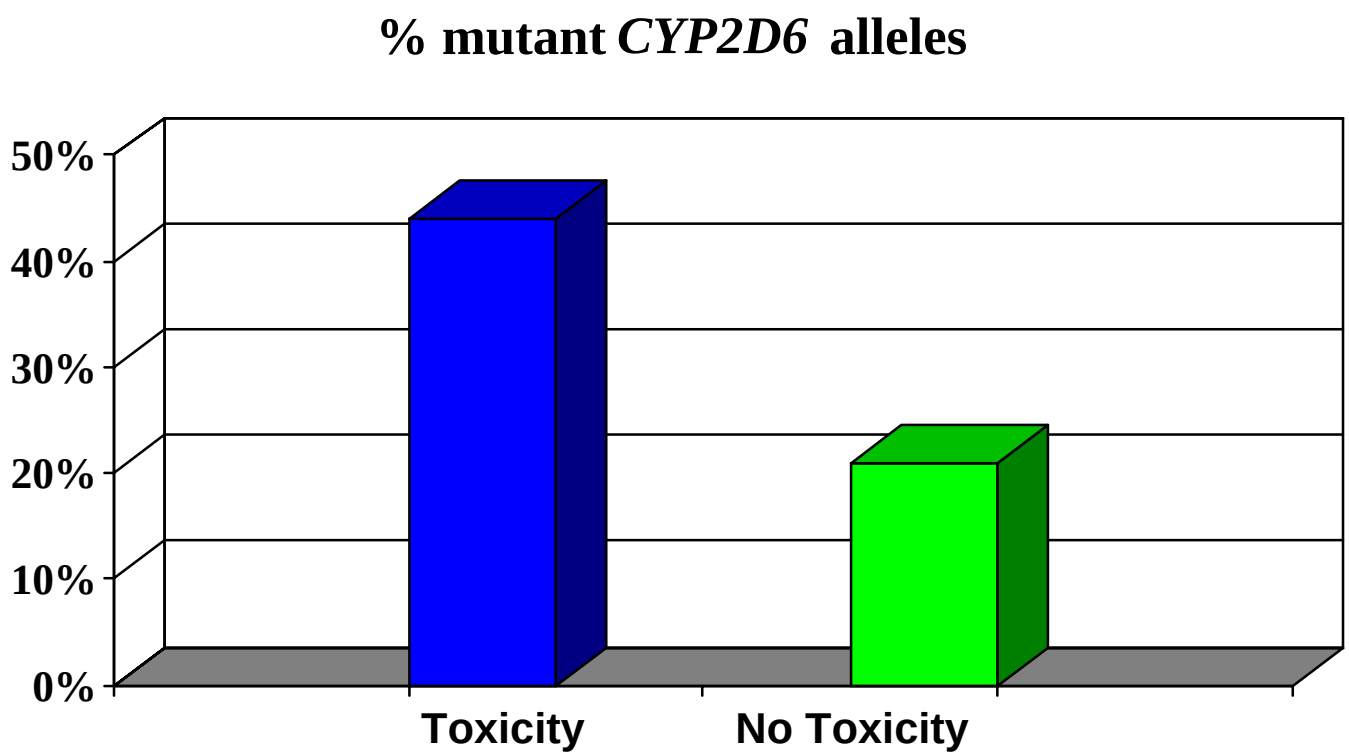
Nortriptyline: inhibits norepinepherine reuptake

muscarinic receptors → side effects

E-10-OH-Nortriptyline: accumulates (M/P > 1) and inhibits NE reuptake

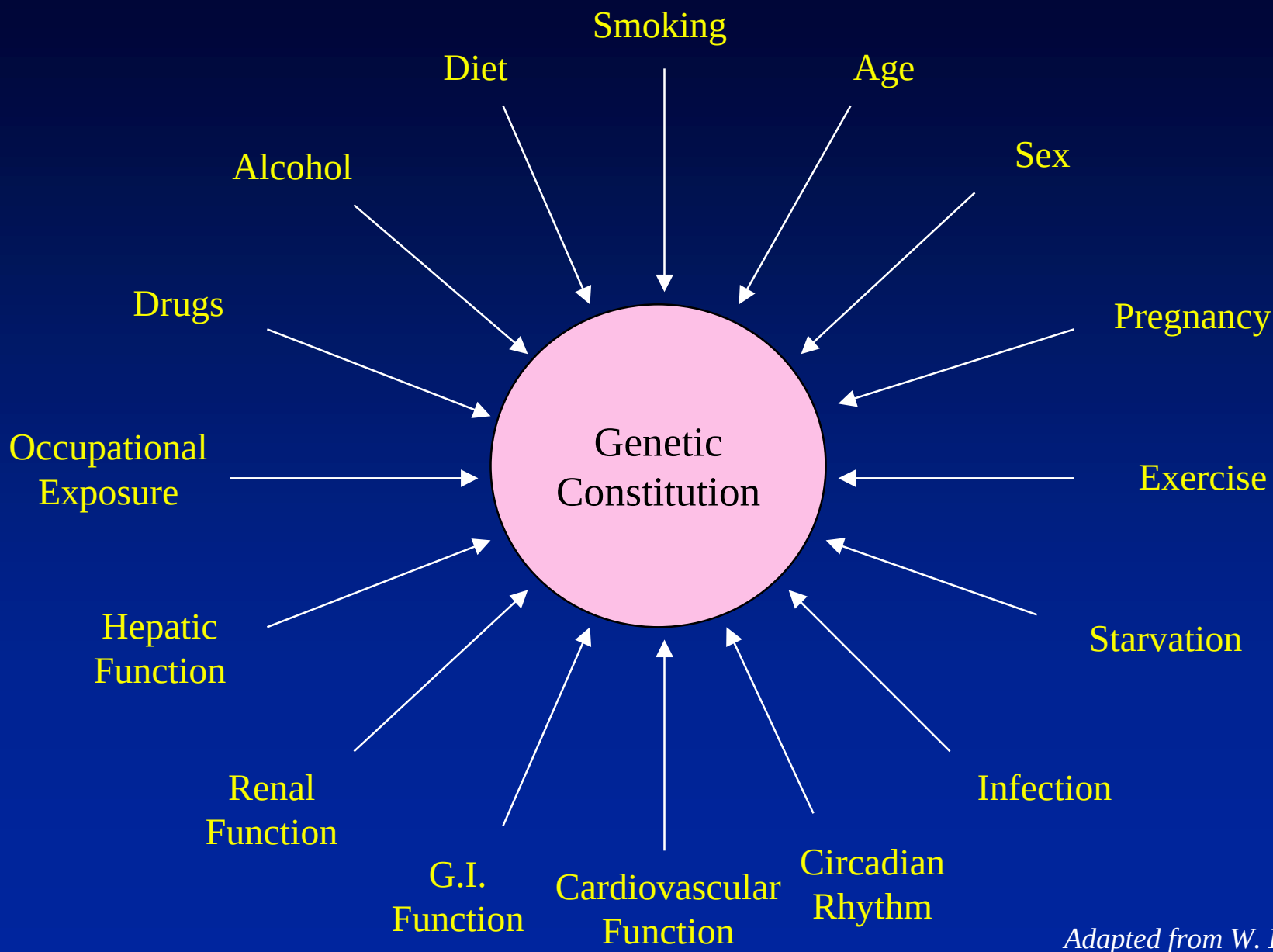
less anticholinergic effect than parent

CYP2D6 genotypes and tricyclic antidepressant toxicity



Chen, Wedlund, et al, CPT 1996

Sources of Interindividual Variability in Enzyme Expression



Adapted from W. Evans, St. Jude

Direction of the Drug Industry

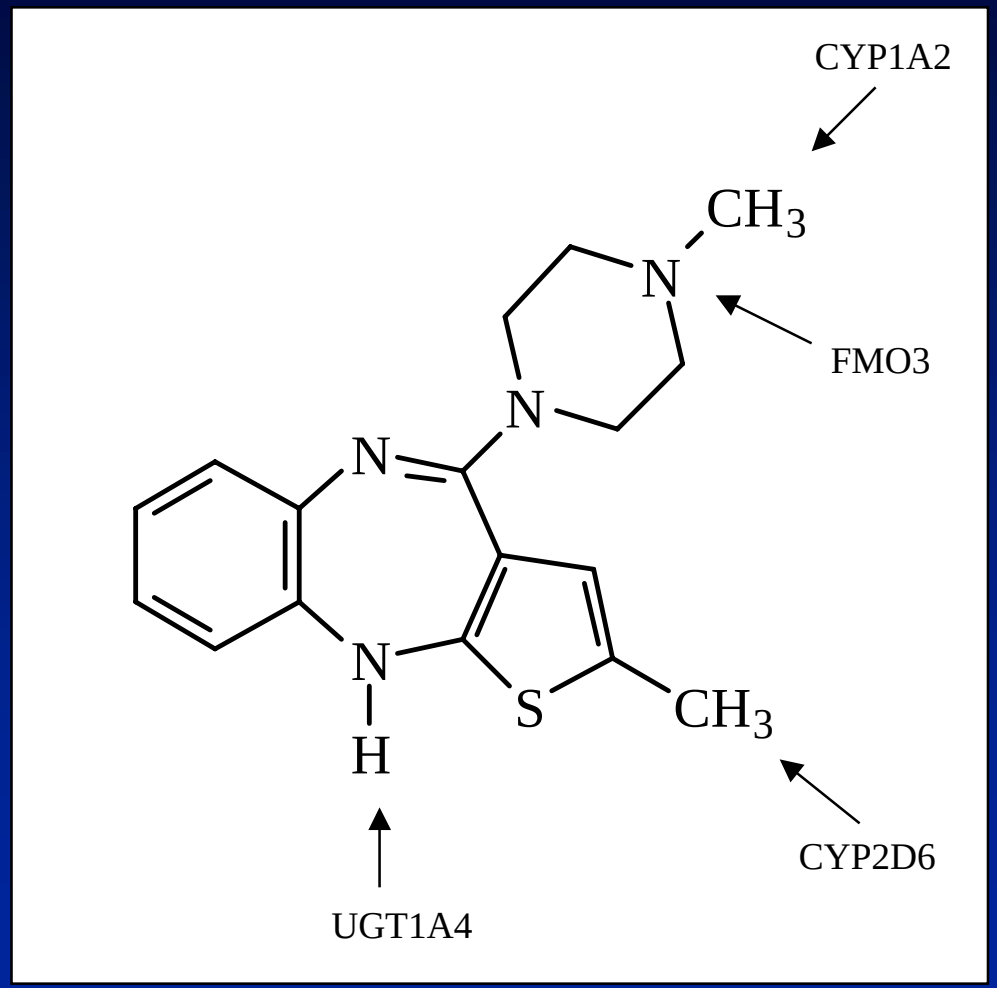
Develop a drug with the following properties:

- Eliminated by multiple pathways (i.e., renal, phase I and phase II), with no one route dominating the clearance
- No active metabolites, if possible
- Limited “special populations” – “Safe for All”

Olanzapine Metabolic Disposition

- 2nd generation antipsychotic

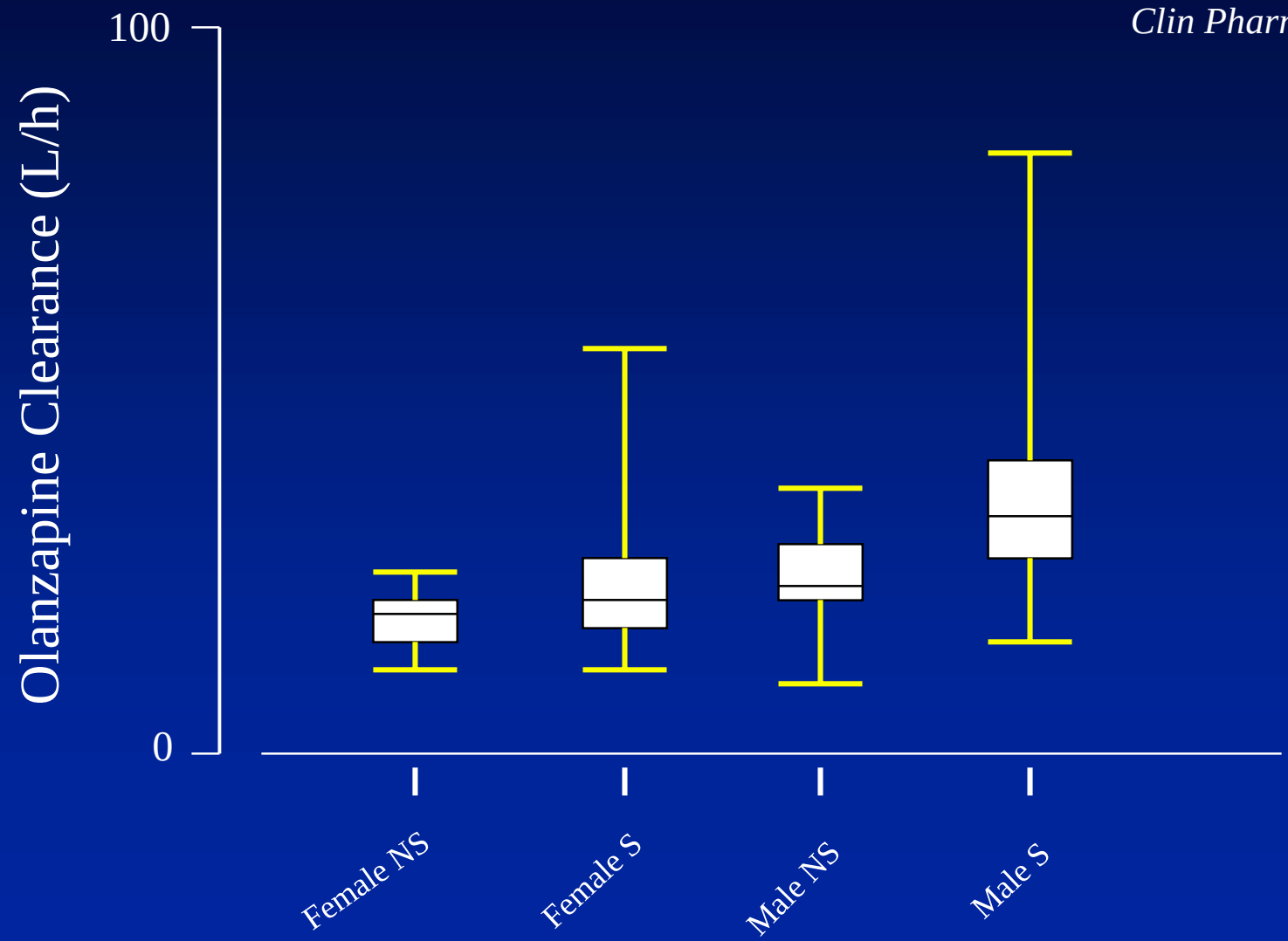
Urine Recovery (% dose)	
10-*N*-glucuronide	28.6%
Olanzapine	17.7%
2-Carboxy OLZ	5.2%
N-Oxide OLZ	3.9%
N-Desmethyl OLZ	0.8%



Adapted from: Ring et al. JPET, 1996

Distribution Plot: Olanzapine Metabolic Clearance

Adapted from Callaghan et al. Clin Pharmacokinet, 1999



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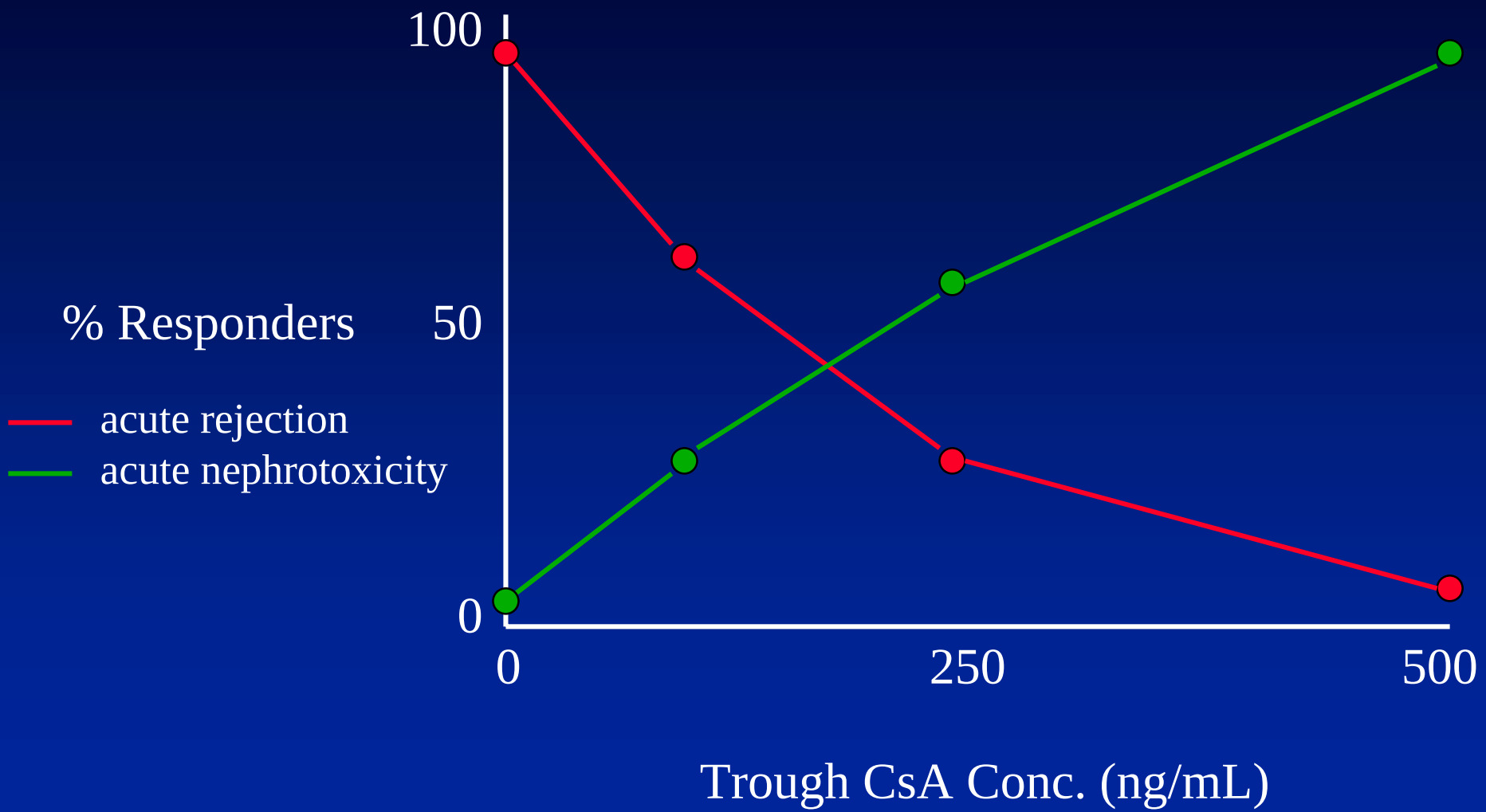
If individualization of pharmacological response is that critical, just measure circulating drug concentrations!

Caveats:

- Timing of results relative to clinical decisions
- One chance to get the drug dose right

Cyclosporine Therapeutic Response: Renal Transplant



Adapted from Kahan, 1988

Future for Genetics and Immunosuppression Therapy

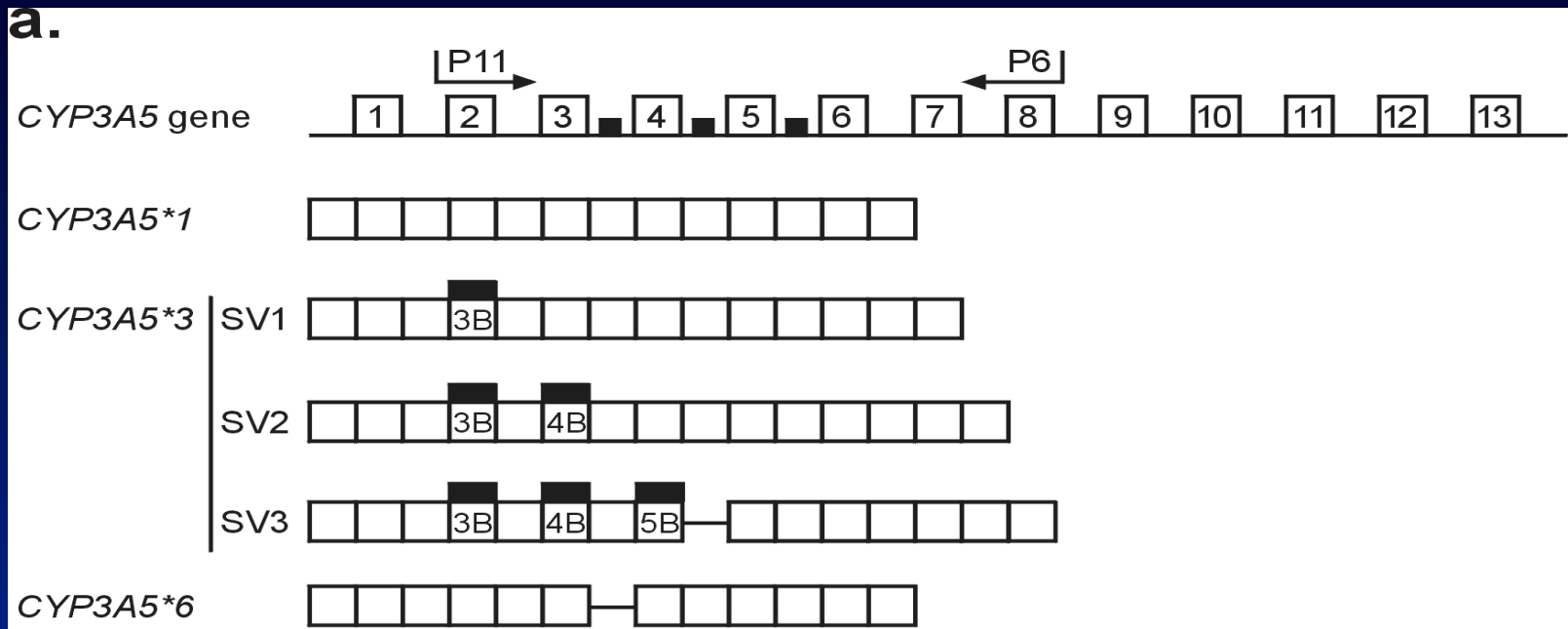
- Therapeutic blood level monitoring is routine
- 5 year Tx survival: liver and kidney, 85% (UWMC)
- Toxicity from long-term immunosuppression therapy increasingly apparent
  - Renal toxicity (cyclosporine, tacrolimus)
  - Hyperlipidemia/hypertension (rapamycin)
  - Osteoporosis/diabetes (steroids)
- No test to predict “at risk” patients
- No test to predict immune tolerance

Is chronic renal dysfunction related to intra-renal immunosuppressant disposition and is there a genetic risk factor?

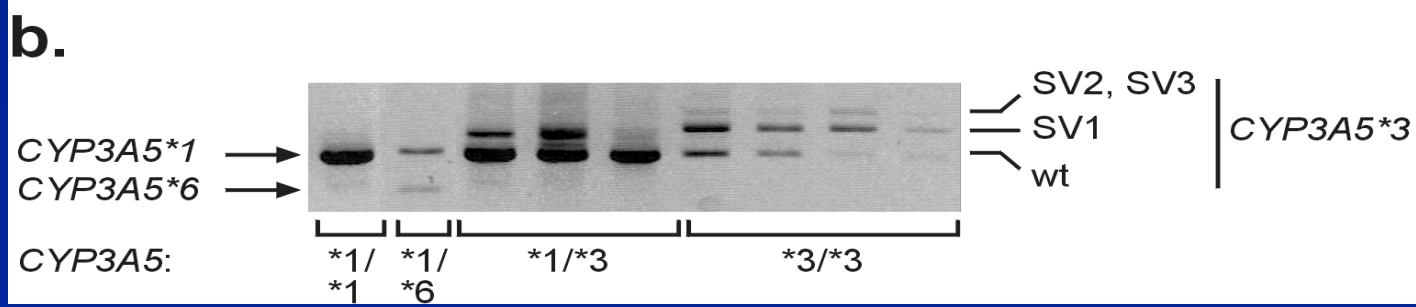
Consider:

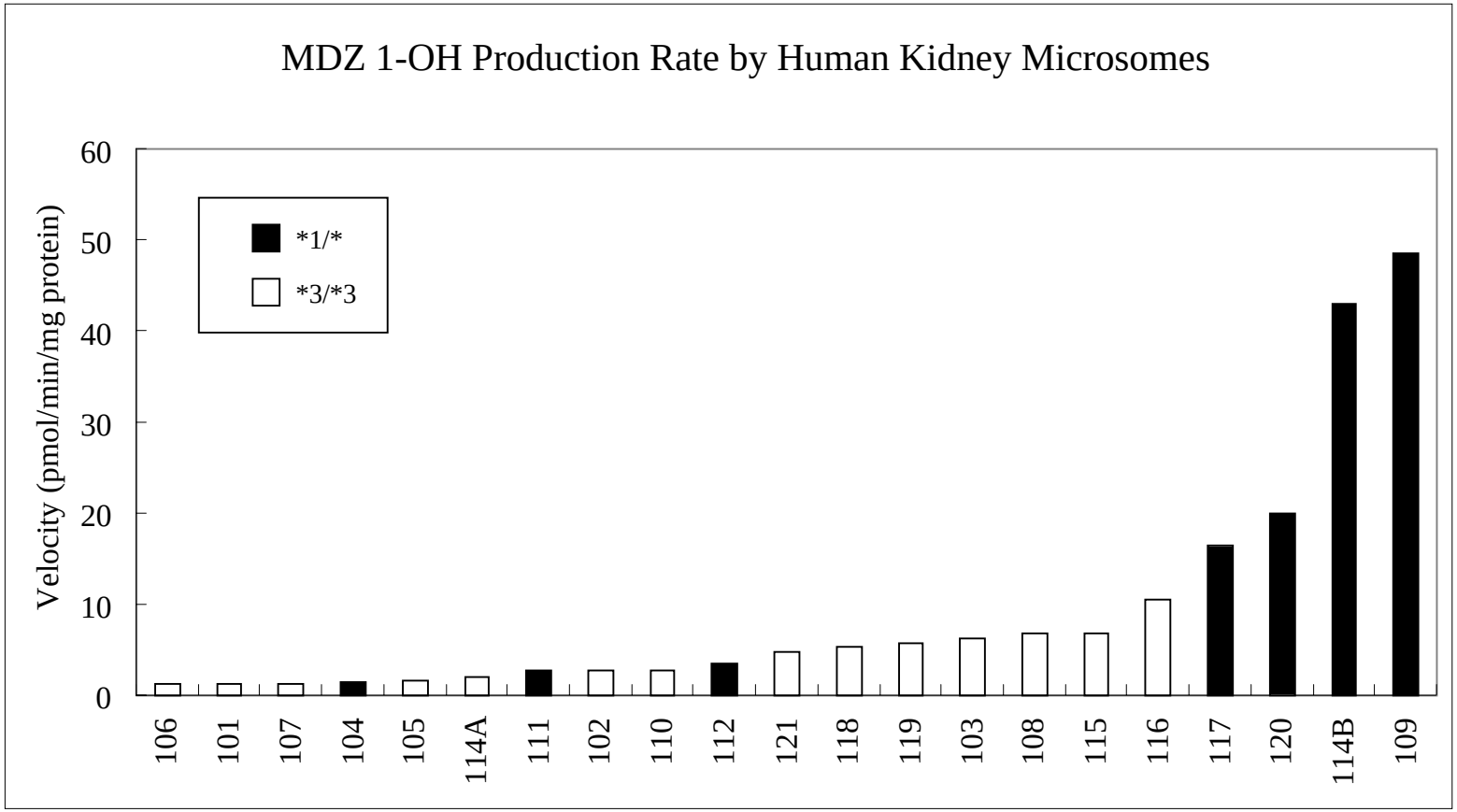
- CYP3A5-mediated oxidation
- P-glycoprotein-mediated efflux

Detection of *CYP3A5* mRNA Splice Variants



Kuehl et al, Nature Genetics, 2001




MDZ 1-OH Production Rate by Human Kidney Microsomes
Velocity (pmol/min/mg protein)
60
50
40
30
20
10
0
1/
*3/*3
106
101
107
104
105
114A
111
102
110
112
121
118
119
103
108
115
116
117
120
114B
109

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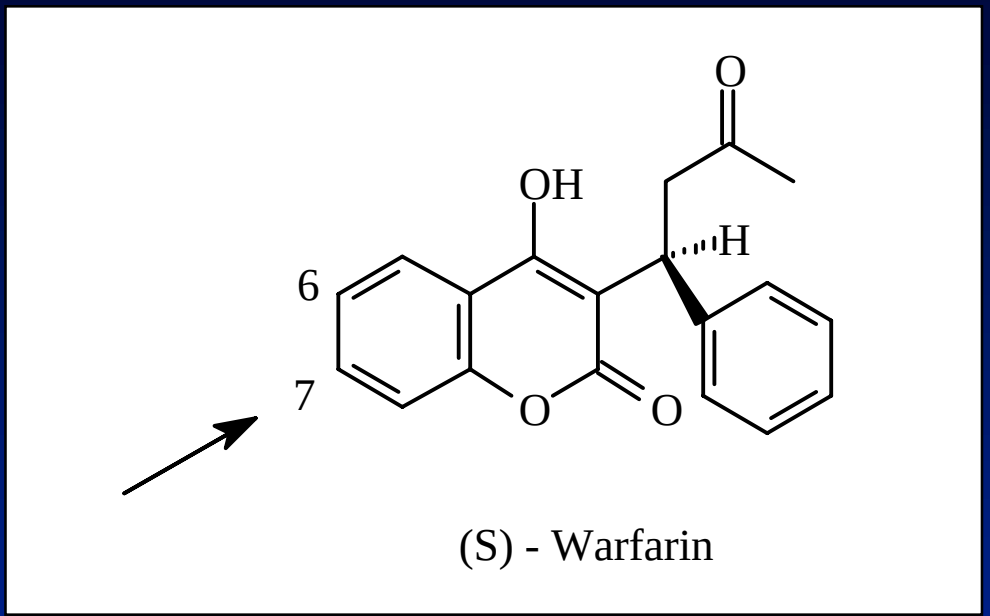
Warfarin and Anticoagulation Therapy

- Most active enantiomer, *S*-warfarin, is cleared exclusively by polymorphic CYP2C9.



(S) - Warfarin

- Drug is dosed to achieve “tolerable” toxicity (impaired clotting)
- Morbidity and mortality can be considerable, even in the best clinic using therapeutic effect monitoring.

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Some ELSI Issues for Consideration

- Information is personal, familial and communal - Who is informed of results?
- Who will have access to pharmacogenetic information?
- How will the information be used (probabilistic nature of pharmacogenetic information)?
- Pharmacogenetic results (drug response) may also impact disease susceptibility (environmental risk).
- Selection of Phase I research subjects based on genotype (equitable risk?)

Summary

Pharmacogenetic testing will undoubtedly be clinically useful, guiding drug selection and dosage decisions.

Will it become essential?

"Here's my sequence..."

New Yorker

Acknowledgments

U. of Washington

Allan Rettie

Dave Veenstra

Mary Hebert

Anna Mastroianni

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William Evan

Erin Schuetz